Amendment to the Claims

This listing of claims will replace all prior versions and listings of claims in the above-referenced application

Listing of Claims:

1. (Withdrawn) An agent for preventing idiopathic thrombocytopenic purpura (ITP) comprising, as an active ingredient, a substance inhibiting interaction between gp39 on a T cell surface, which is a receptor mediating contact-dependent helper effector function, and CD40 on an antigen-presenting cell surface.

2. (Withdrawn) The agent for preventing ITP according to Claim 1, wherein the substance is an anti-gp39 antibody.

3. (Original) A method of preventing onset of idiopathic thrombocytopenic purpura (ITP), comprising administering to a candidate for the prevention a substance inhibiting interaction between gp39 on a T cell surface and CD40 on an antigen-presenting cell surface in an amount effective to prevent onset of ITP, said gp39 being a receptor which mediates a contact-dependent helper-effector function.

4. (Original) The method according to Claim 3, wherein the substance is an anti-gp39 antibody.

5. (Currently Amended) The method according to Claim 3, wherein the administration of the substance is initiated ~~when the number of platelets in the candidate does not decrease~~ before an immune response to platelets begins to occur.

Remarks

I. Summary of Claim Amendments

Applicants have amended Claim 5 to indicate that the substance that inhibits the interaction between gp39 and CD40 on an antigen-presenting cell is administered before an immune response to platelets begins to occur. Support for this amendment can be found on page 2, paragraph 1 and lines 19-25 of the specification.

II. Rejection of Claim 5 Under 35 U.S.C. § 112, First Paragraph

The Examiner states that the specification does not provide support for the limitation "wherein the administration of the substance is initiated when the number of platelets in the candidate does not decrease."

Applicants have replaced this phrase with the limitation that the substance must be administered before an immune response to platelets begins to occur, and have pointed out where the specification, as filed, provides support for the new limitation. Therefore, in view of the amendment to Claim 5, Applicants respectfully request that the rejection be reconsidered and withdrawn.

III. Rejection of Claim 5 Under 35 U.S.C. § 112, Second Paragraph

The Examiner states that the phrase "wherein the administration of the substance is initiated when the number of platelets in the candidate does not decrease" in Claim 5 is indefinite, because the number of platelets in an individual ITP patient may vary. The Examiner also states that the specification does not provide a standard for ascertaining the requisite degree.

Applicants have amended Claim 5 to replaced this phrase with the limitation that the substance must be administered before an immune response to platelets begins to occur. On page 12, Example 3 of the specification, Applicants provide a method of determining the anti-platelet antibody titer in the plasma of a mammal that could readily be adapted for use with human subjects to determine whether an immune response to platelets has begun to occur. In addition, Applicants have provided an example of human subjects that are susceptible to acquiring ITP and who may be candidates for prophylactic administration of a substance that inhibits the interaction between gp39 and CD40 on an antigen-presenting cell (see page 2, lines 10-15 of the specification and Exhibit A, Williams, *et al.*, *British Journal of Haematology*

(1998), *101*:779-782 at the result section on pages 780-781). Thus, a person of skill in the art would be able to determine whether or not an immune response to platelets has begun to occur and what population might be susceptible to developing ITP using the guidance of Applicants' specification.

IV. Rejection of Claims 3-5 under 35 U.S.C. § 102(b) Over Kalled, *et al.*, WO 98/39026 (hereinafter "Kalled")

A. Summary of the Examiner's Rejection

The Examiner states that Kalled teaches a method of treating ITP with anti-CD40L antibodies (also called "anti-gp39 antibodies). The Examiner believes that Kalled inherently discloses treating ITP during remission because Kalled teaches administering a therapeutically effective amount of an anti-CD40L antibody.

B. Summary of Applicants' Claimed Invention

Applicants claim a method of preventing the onset of ITP by administering to a candidate a substance, such as an anti-gp39 antibody, that inhibits the interaction between gp39 on a T cell surface and CD40 on an antigen-presenting cell surface. The substance may be administered before an immune response to platelets begins to occur.

C. Summary of Kalled

Kalled teaches a method of treating immune related disorders, such as ITP, by administering an anti-CD40L compound (Kalled, page 2, 16-18). Kalled does not teach administering anti-CD40L compound to prevent the onset of ITP.

D. Kalled Does Not Teach Every Element of the Claims

The Federal Circuit has stated that "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987).

Kalled does not disclose a method of preventing the onset of ITP by administering an anti-CD40L compound before the onset of ITP, but instead teaches a method of treating immune-related diseases after the onset of the disease. In particular, Kalled does not disclose

administering an anti-CD40L compound before an immune response to platelets begins to occur. As admitted by the Examiner, Kalled teaches administering a "therapeutically effective" amount of anti-CD40L antibodies (see Office Action dated February 24, 2003, page 5, lines 8-13). The term "therapeutically effective" is not defined in Kalled. However, the plain meaning of the term "therapeutic" is "having or exhibiting healing powers" (see Exhibit B, American Heritage College Dictionary, page 1406). Thus, Kalled indicates that the anti-CD40L compounds are administered to heal a subject suffering from a disease related symptom and not to prevent the onset of such symptoms. If no symptoms had occurred, no healing would be required, and Kalled would have stated that a prophylactic amount, not a therapeutic amount, of an anti-CD40L antibody was administered. Therefore, Kalled does not teach or suggest all of the limitations of Applicants' claims.

The Examiner states that given the teachings of administering therapeutically effective amounts of anti-CD40L antibodies on pages 9-11 of Kalled, it would have been inherent in treating ITP patients with anti-CD40L antibodies to prevent the onset of ITP during remission. However, Kalled discloses that when symptoms of an immune-related disease have been alleviated to the desired level, treatment with the anti-CD40L antibodies may cease and that treatment can be resumed when symptoms reoccur (see Kalled, page 10, lines 20-22). Thus, Kalled teaches that when a patient is in remission, treatment with anti-CD40L antibodies can cease but after the patient relapses, treatment can resume. This contradicts the Examiner's assertion that Kalled inherently teaches treating ITP patients during remission of the disease.

The Federal Circuit has stated that "Anticipation by inherent disclosure is appropriate only when the reference discloses prior art that must necessarily include the unstated limitation . . ." *Transclean Corp. v. Bridgewood Services, Inc.*, 62 U.S.P.Q.2d 1865, 1871 (Fed. Cir. 2002). Kalled does not disclosed that ITP may be treated before the onset of the disease, including before the onset of the disease after a period of remission. Instead, Kalled teaches treatment of ITP after the onset of the disease (see Kalled, page 13, lines 23-25 and timing of treatment in Experiments II, V and VII on pages 13-14) and that treatment may cease when the symptoms of the disease are alleviated. Thus, Kalled does not anticipate Claims 3-5, because the method of treating ITP disclosed by Kalled does not of necessity include the unstated limitation that ITP is treated during periods of remission to prevent reoccurrence of the disease, but instead teaches that when the symptoms of the disease are alleviated that treatment can cease. Therefore, Kalled

does not anticipate Applicants' Claims 3-5 because Kalled does not teach treating ITP before the onset of the disease, and Applicants respectfully request that the rejection be reconsidered and withdrawn.

V. Rejection of Claims 3-5 under 35 U.S.C. § 102(e) Over Black, *et al.*, U.S. Patent No. 6,001,358 (hereinafter "Black")

A. Summary of the Examiner's Rejection

The Examiner states that Black teaches methods of treating ITP with anti-gp39 antibodies. The Examiner believes that Black inherently discloses treating ITP during remission because Black teaches administering anti-gp39 antibodies for therapeutic or prophylactic immunosuppression.

B. Summary of Black

Black teaches a method of treating ITP by administering an anti-gp39 antibody to a patient (Black, Col. 14, lines 33-42). In addition, Black suggests that administration of anti-gp39 antibodies may be used to prevent ITP (Black, Col. 33, lines 23-31). However, Black does not provide any experimental evidence that ITP can be prevented by administering anti-gp39 antibodies. In addition, Black does not indicate how to select a patient in need of prophylactic administration of anti-gp39 antibodies.

C. Black Does Not Enable Preventing ITP

The Federal Circuit has stated that "A § 102(b) reference 'must sufficiently describe the claimed invention to have placed the public in possession of it.'" *Paperless Accounting, Inc. v. Bay Area Rapid Transit Sys.*, 231 U.S.P.Q. 649, 653 (Fed. Cir. 1986). Black does not teach how to select a patient in need of prophylactic administration of anti-gp39 antibodies. Nor does Black provide any experimental supporting the suggestion that ITP can be prevented in a mammal by administration of an anti-gp39 antibody that could be used as guidance by a person of skill in the art as to what parameters are important in the prevention of ITP. Thus, Black does not provide an enabling disclosure of preventing ITP using anti-gp39 antibodies. In particular, Black does not disclose treating ITP before an immune response to platelets begins to occur, such as claimed by Applicants in Claim 5, as amended.

Since Black does not provide an enabling disclosure of how to prevent ITP by administering anti-gp39 antibodies to a patient, Black does not anticipate Claims 3-5, and Applicants respectfully request that the rejection be reconsidered and withdrawn.

VI. Rejection of Claims 3-5 under 35 U.S.C. § 102(e) Over Lederman, *et al.*, U.S. Patent No. 5,993,816 (hereinafter "Lederman")

A. Summary of the Examiner's Rejection

The Examiner states that Lederman teaches a method of treating ITP with 5C8-specific antibodies (gp39-specific antibodies). The Examiner believes that Lederman inherently discloses treating ITP during remission because Lederman teaches administering a effective amounts of the gp39-specific antibody.

B. Summary of Lederman

Lederman teaches a method of inhibiting an immune response in an animal suffering from an autoimmune disease, such as ITP, (Lederman, Col. 11, lines 27-35) by administering an antibody that specifically recognizes the activated T Cell surface protein, CD40 ligand (Lederman, Col. 2, lines 15-18 and Col. 10, lines 60-65). Lederman does not teach administering the antibody to prevent the onset of ITP.

C. Lederman Does Not Teach Every Element of the Claims

Lederman does not disclose a method of preventing the onset of ITP by administering an anti-CD40L antibody before the onset of ITP, but instead teaches a method of treating immune related diseases after the onset of the disease. In particular, Lederman does not disclose administering an anti-CD40L antibody before an immune response to platelets begins to occur. Therefore, Lederman does not teach or suggest all of the limitations of Applicants' claims.

The Examiner states that given the teachings of Lederman of administering effective amounts of anti-CD40L antibodies to inhibit T cell activation of B cells, it would have been inherent in treating ITP patients with anti-CD40L antibodies to prevent the onset of ITP during remission. However, Lederman teaches that anti-CD40L antibodies should be administered to animals suffering from an autoimmune disease (Lederman, Col. 11, lines 27-35). The use of the term "suffering" in the disclosure of Lederman indicates that the animal has some pain or

distress (see Exhibit C, American Heritage College Dictionary, page 1357), and thus must already have the disease and be suffering from the symptoms of the disease. There is no disclosure in Lederman that the onset of an autoimmune disease can be prevented by administering to an animal anti-CD40L antibodies.

The Federal Circuit has stated that "Anticipation by inherent disclosure is appropriate only when the reference discloses prior art that must necessarily include the unstated limitation . . ." Transclean Corp. v. Bridgewood Services, Inc., 62 U.S.P.Q.2d 1865, 1871 (Fed. Cir. 2002). Lederman does not disclosed that ITP may be treated before the onset of the disease, including before the onset of the disease after a period of remission. Instead, Lederman teaches treatment of ITP after the onset of the disease when an animal is suffering from the symptoms of the disease. Thus, Lederman does not anticipate Claims 3-5, because the method of treating ITP disclosed by Lederman does not of necessity include the unstated limitation that ITP is treated during periods of remission to prevent reoccurrence of the disease, but instead teaches that anti-CD40L antibodies should be administered after the animal is suffering from the disease. Therefore, Lederman does not anticipate Applicants' Claims 3-5 because Lederman does not teach treating ITP before the onset of the disease, and Applicants respectfully request that the rejection be reconsidered and withdrawn.

VII. Rejection of Claims 3-5 under 35 U.S.C. § 103(a) Over Kalled and/or Black and/or Lederman in View of Nemoto, *et al.*, British Journal of Haematology (1995), 91:691-696 (hereinafer "Nemoto") or Medical Letter on Drugs and Therapeutics (1996), 38:6-8 (hereinafter "Medical Letter") or Williams, *et al.*, British Journal of Haematology (1998), 101:779-782 (hereinafer "Williams")

A. Summary of the Examiner's Rejection

The Examiner states that Kalled, Black and Lederman teach administering anti-CD40L antibodies to treat and/or prevent ITP in patients.

The Examiner states that Nemoto teaches the use of an immunosuppressant to prevent the development of thrombocytopenia and suppress the increase in circulating antibodies against platelets in an experimental animal model of ITP and that an immunosuppressant in combination

with steroids would suppress the production of antibodies and phagocytic function in treating ITP patients.

The Examiner states that Medical Letter teaches that acute and chronic ITP can be treated with Rho(D) immune globulin, as well as with IVIG and sometimes with a splenectomy, and that platelet counts increase after treatment and maintenance treatment would be helpful.

The Examiner states that Williams teaches Fcγ RIIIa polymorphisms are implicated in the pathophysiology of ITP and that platelet antigens are targeted in this disease and that the destruction of antibody sensitized platelets are involved in the disease.

The Examiner believes given the immunosuppressive properties of anti-CD40L antibodies disclosed in Kalled, Black, and Lederman, a person of ordinary skill in the art would have been motivated to provide anti-CD40L antibodies to treat ITP in combination with known treatments in order to inhibit and prevent immune responses to platelets in ITP patients. The Examiner also states that given the disclosure of Williams, one of ordinary skill in the art would have been motivated to provide anti-CD40L antibodies in certain targeted patient populations to protect against more severe disease.

B. Summary of Nemoto

Nemoto teaches the use of deoxyspergualin (DSG) to suppress thrombocytopenia in male W/BF1 mice, a strain of mice that develops sever thrombocytopenia if untreated. Nemoto teaches that DSG suppresses the production of anti-platelet autoantibodies which cause thrombocytopenia (Nemoto, page 695, Col. 2, lines 14-16). Nemoto suggests that DSG in combination with steroids may be useful as a new therapy for patients with ITP (Nemoto, page 695, Col. 2, lines 22-26).

C. Summary of Medical Letter

Medical Letter teaches that Rho(D) antigen is responsible for most cases of Rh sensitization which occurs when Rh-positive fetal red blood cells enter the maternal circulation of an Rh-negative woman and that injection of anti-D globulin can prevent immunization of the mother (Medical Letter, page 7, lines 3-7).

Medical Letter also teaches that anti-D globulin can be used to treat Rh-positive ITP patients because the anti-D coats the patient's D+ red blood cells with antibody, and as these

coated red blood cells are cleared by the spleen, they saturate the capacity of the spleen to clear antibody-coated cells. Thus, antibody coated platelets are spared (Medical Letter, page 7, lines 8-10).

D. Summary of Williams

Williams teaches that the gene for FcγRIIA is polymorphic and that polymorphic variation of FcγRIIA is due to a single base substitution which cause amino acid 131 to be either histidine or arginine. Patients with sever ITP show a statistically significant skewing toward the FcγRIIA-RR131 allotype (see Williams, page 781, Col. 1, lines 9-11).

E. The Combination of the References Does Not Teach All of the Claim Limitations

As discussed above, Kalled, and Lederman do not teach preventing the onset of ITP by administering a substance that inhibits the interaction between gp39 and CD40, and Black fails to disclose an enabled method of preventing the onset of ITP. Nemoto does not remedy the deficiencies of Kalled, Black and Lederman because Nemoto also does not teach or suggest preventing the onset of thromocytopenia by treating a patient with DSG but instead teaches that DSG, in combination with steroids, may be a useful therapy for in treating patients who already have ITP. Treatment of ITP with steroids involves weaning the patient off of the steroids once the patient is in remission (see Exhibit D, Lahita, *Texbook of the Autoimmune Diseases* (2000), page 198, Col. 2, lines 14-25). Since Nemoto states that DSG should be used in combination with steroids and ITP patients are taken off of steroids during remission, Nemoto teaches that the immunosuppressant DSG should be discontinued when an ITP patient is in remission. Thus, Nemoto does not teach the use of an immunosupressant in preventing ITP and teaches away from the use of an immunosuppressant once an ITP patient is in remission. Therefore, the combination of Kalled, Black, Lederman and Nemoto does not render Applicants' Claims 3-5 obvious.

Moreover, Medical Letter does not remedy the deficiencies of Kalled, Black and Lederman because Medical Letter also does not teach or suggest preventing the onset of thromocytopenia by treating a patient with an immunosuppressant. Medical Letter teaches that a patient with ITP should be administered an antibody that will bind to their red, not that antibody production by B cells should be suppressed. Thus, Medical Letter teaches away from the use of

an immunosuppressant that inhibits antibody production by B cells, such as an anti-CD40L antibody. Since Medical Letter teaches away from the use of a substance that would decrease antibody production, the combination of Kalled, Black, Lederman and Medical Letter does not render Applicants' Claims 3-5 obvious.

In addition, Williams does not remedy the deficiencies of Kalled, Black and Lederman because Williams also does not teach or suggest preventing the onset of thromocytopenia by treating a patient with an immunosuppressant, and, in fact, the only method of treating ITP mentioned by Williams is a splenectomy (Williams, page 779, Col. 1, first paragraph after the abstract). A splenectomy would not be performed on an ITP patient in remission as a means for preventing a relapse since splenectomies are given to ITP patients only when they do not respond to treatment with steroids or when they have frequent relapses (see Exhibit D, Lahita, *Texbook of the Autoimmune Diseases* (2000), page 198, Col. 2, lines 33-34). Since Williams does not teach or suggest any method of preventing the onset of ITP, the combination of Kalled, Black, Lederman and Williams does not render Applicants' Claims 3-5 obvious.

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Respectfully submitted,

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